Clean copy of changed paragraphs:

Figure 3A: Physical map of the CSNB1 minimal region indicating the location of overlapping BACs and PACs (short lines) and the chromosomal position of several genes in this region, including *NYX*. The lower horizontal line demonstrates the genomic organization of *NYX*, showing that it is comprised of three exons, with a translation start site in the second exon, a stop codon in the third exon and a polyadenylation sequence in the 3' untranslated region. Figure 3B: The amino acid sequence (SEQ ID NO.: 2) of nyctalopin shows homology with members of the SLRP family of proteins. The protein has 11 leucine-rich repeat motifs with a 24 amino acid consensus for small leucine-rich proteoglycans with cysteine clusters flanking the repeat core of the protein. The conserved amino acids are shown in bold. Figure 3C: Dendogram showing the predicted relationship among members of SLRP. Chondroadherin (CHAD) and nyctalopin appear to represent a fourth class (IV) within SLRP.

Characteristics of Nyctalopin

NYX encodes a 481 amino acid protein, herein called nyctalopin, which has sequence similarity with members of the superfamily of proteins containing tandem arrays of the leucine-rich repeat (LRR) motif [10,13]. Such proteins are known to function in protein-protein interactions, especially in matrix assembly, and therefore nyctalopin may possibly be mediating specific neural connections between cells in the retina. Moreover, the presence of the 24 amino acid consensus: x-x-I/V/L-x-x-x-x-F/P/L-x-x-L/P-x-x-L-x-x-L/I-x-L-x-x-N-x-I/L (where I,V,L,F,P and N are single letter amino acid codes and "x" represents any amino acid) in the core protein with cysteine clusters flanking the LRR domain (see Figure 3B), qualifies nyctalopin as a new member of the subfamily of small leucine-rich proteoglycans (SLRPs) [10]. From a homology comparison of nyctalopin with other SLRP proteins, it is evident that nyctalopin is a unique member of this subfamily and the LRR superfamily in general. Nyctalopin has five putative consensus sequences (N-X-(S/T)) necessary for substitution by N-linked oligosaccharides or keratan sulfate [14], three of these sequences lie within the LRR region. The NH_2-terminal end of nyctalopin is predicted [15] to contain a membrane signal peptide with a putative cleavage site between amino acid 23 and 24, AWA-VG (Figure 3). In addition, the carboxyl-terminal region of nyctalopin contains a GPI-anchor signal sequence,

including the requisite GPI N-terminal signal sequence (amino acids 339 to 379), the C-terminal hydrophobic region (last 22 amino acids) and a potential cleavage site at amino acids 445-447 [16] (Fig. 3B). The identification of these sites was accomplished at the Expasy™ website, and is well known to those skilled in the art. Thus, *NYX* codes for a GPI-anchored proteoglycan with a putative membrane signal peptide. Without being limited to a theory, these results suggest that the clinical features of complete X-linked CSNB can be explained by the presence of a mutant nyctalopin (or entire absence of nyctalopin) causing the disruption of selected connections or interactions between retinal neurons, including those of the retinal ON-bipolar pathway, possibly during early stages of embryonic development.

BAC clone 378P5 (Fig. 3A) yielded a sequence that had partial complete homology with a 526-bp expressed sequence tag Q14392 (Accession No. AI861796). Sequence of the BAC clone 378P5 in the region of homology to ESTQ14392 overlaps with the partial DNA sequence from BAC clone 169I5(Fig. 3A). GenScan™ and GeneFinder™ analysis of a 20 kb portion of the genomic sequence from clone 169I5 (Sanger Centre) that encompasses EST Q14392 predicted a novel open reading frame which we have designated *NYX* and is shown in Figure 3A.